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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/803,521	03/17/2004	Daniel P. Wermeling	INT-002C1CP	5461

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EXAMINER	
YU, GINA C	

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1617	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/803,521	WERMELING, DANIEL P.	
	Examiner	Art Unit	
	GINA C. YU	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-18,20 and 27-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-18,20 and 27-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *01/31/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of amendment filed on January 31, 2008.

Claim rejection made under 35 U.S.C. § 112, second paragraph, as indicated in the previous Office action, is withdrawn in part in view of the claim amendment.

Claim rejections made under 35 U.S.C. § 103(a) are withdrawn in view of further consideration.

Applicants' request to hold the obviousness double patenting rejections in abeyance until allowance of the claims has been noted, and the rejections are maintained for the reasons of record.

New rejections are made to address a new claim. Claims 11-18, 20, 27-29 are pending.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 29 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 29 recites that the composition of claim 1 contains "no less than 25 mg/mL midazolam or pharmaceutically acceptable salt thereof". The new weight limitation here is not supported by applicant's original disclosure; the specification discloses composition comprising 25 mg/ml midazolam on pages 15 and 22, but fails to support compositions containing a higher concentration of midazolam or its salts. Since the amended limitation encompasses midazolam concentrations that are greater than 25 mg/mL, the amendment introduces new matter which is not supported by the original disclosure.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 11, 13, 15, 18, 20, 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schweizer (US 5,166,202) in view of Hjortkjaer et al. (J. Pharm. Pharmacol. 1999, 51: 377-383) and Haslwanter et al. (US 6565832 B1).

Schweizer teaches a method of treating panic disorder, panic attacks and the prevention of panic attacks to reduce anxiety by nasally administering midazolam and its pharmaceutically acceptable salts. The reference teaches administering 1-4 drops of an aqueous solution of midazolam, which is equivalent to 0.05-0.2 ml of the active ingredient. See col. 4, lines 41 – 53; instant claim 4. The reference teaches a nasal suspension in col. 3, lines 63- 66, meeting instant claim 7. Inducing general anesthesia by administering midazolam with other anesthetic agent is also taught. See col. 3, lines 8 – 10; instant claim 8. With respect to claim 18, it is obvious that the level of plasma

concentration achieved by a specific dosage is the result of administering midazolam to the subject.

Although Schweizer does not specifically indicate the formulation of the nasal composition, the reference teaches using pharmaceutically acceptable nasal carriers that are well known in the art. See col. 3, lines 56 – 68. Particularly mentioned are glycols and glycol ethers for carriers.

Hjortkjaer teaches that polyethylene glycol 400 has been tested as a safe solvent and carrier for benzodiazepines and other non-irritating drugs for short-term use in man.

Haslwanter teaches an aqueous nasal spray formulation which exhibits increased retention in the nasal cavity. The composition comprises up to about 10 % by weight/volume of polyethylene glycol. See col. 3, line 50 – col. 4, line 56. The reference also teaches that sterile water is used to prevent microbial contamination. See col. 2, lines 55-67. Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." See In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). In this case, it is viewed that there is no significant difference between up to about 10 % by weight or volume of polyethylene glycol and presently claimed about 15 %. Furthermore, Hjorkjaer discloses that safety of using polyethylene glycol as a carrier for benzodiazepines nasal spray has been proven. Thus, discovering an optimal amount of polyethylene glycol as a carrier for

midazolam by routine experimentations would have been obvious to one of ordinary skill in the art.

It would have been obvious to one of ordinary skill in the art at the time of the present invention to modify the teaching of Schweizer by formulating a midazolam nasal composition, as motivated by Hjortkjaer and Haslwanter, because 1) Schweizer specifically teaches to formulate a nasal composition of midazolam as well known in pharmaceutical art; 2) Hjortkjaer teaches that polyethylene glycol is a safe solvent and used as a carrier for benzodiazepines; and 3) Haslwanter teaches a general aqueous nasal spray formulation for medicaments, which exhibits increased retention in the nasal cavity. The skilled artisan would have had a reasonable expectation of successfully producing a stable and safe nasal formulation comprising midazolam with increased drug retention in the nasal cavity.

With respect to claims 16-19, the limitations are directed to the metabolism rate of the midazolam-containing composition. It is viewed that the obvious variation of the prior arts, which would comprise midazolam in a nasal carrier comprising polyethylene glycol and propylene glycol, and saccharide, would naturally have the metabolism rate as defined in the present claims.

Claims 14 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schweizer, Hjortkjaer and Haslwanter over claim 11, 13, 15, 18, 27 as above, and further in view of Craig et al. (US 5554639).

Haslwanter teaches in Example 6 a nasal spray composition comprising polyethylene glycol, propylene glycol, glycerine and an active ingredient.

The combined references fail to teach a preservative-free composition.

Craig teaches that a sterile, preservative-free nasal solution is preferred. See col. 3, lines 1 –4. Example formulations show an aqueous sterile composition comprising sodium saccharin and an active ingredient. See Examples 14-17. Using polyethylene glycol 400 for nasal solution is taught in col. 2, lines 53-57. See instant claim 28.

It would have been obvious to one of ordinary skill in the art at the time of the present invention to modify the nasal composition of the combined references to make a preservative-free nasal spray composition as motivated by Craig because it would be more desirable to use sterile formulation without preservatives. The skilled artisan would have had a reasonable expectation of successfully producing a preservative-free, sterile nasal formulation containing midazolam.

Claims 16, 17, 20 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schweizer, Hjortkjaer and Haslwanter over claim 11, 13, 15, 18, 28 as above, and further in view of Fisgin et al. (J. Child Neurol. Dec. 2000).

Schweizer does not teach the time required for midazolam to take effects.

Fisgin discloses a method of rapidly treating acute seizures of children in 5 minutes by nasally administering midazolam (5 mg/mL). See abstract.

It would have been obvious to a skilled artisan to formulate and administer the midazolam nasal spray of the combined references as motivated by Fisgin because the latter teaches the time required for midazolam that is nasally administered to take effects. The skilled artisan would have had a reasonable expectation of successfully

determining the dosage of midazolam and the time required to treat acute by nasally administering midazolam.

Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Schweizer, Hjortkjaer and Haslwanter over claim 11, 13, 15, 18, 28 as above, and further in view of Mukae et al. (US 5789375).

The combined references fail to teach the amount of propylene glycol as required in the instant invention.

Mukae teaches using up to 70 % by volume of glycols to make a nasal composition which is low in irritation and highly absorbed through the nasal mucous membrane. See col. 3, line 40 – col. 4, line 37. The reference teaches that propylene glycol is particularly preferable since it's been practically used as an additive to pharmaceuticals. The reference also teaches that the upper ratio in which alcohols are contained in the composition is determined depending on the kinds of alcohol used, combinations of the alcohols, the effect or advantage to be derived from alcohols, etc. See col. 4, lines 13 – 21. Adding thickeners or gelling agents, such as polyethylene glycol, for enhancing the retentivity of a medicine on the nasal mucosae is also taught. See col. 5, lines 17 – 33.

It would have been obvious to one of ordinary skill in the art at the time of the present invention to modify the nasal composition of the combined references by incorporating the glycols-based vehicle as motivated by Mukae, because the latter teaches using propylene glycol based vehicle for low irritation and high absorption of active drugs. Given the general teaching in Mukae that the amounts of alcohol vary

depending on the types of the drugs and other factors, the skilled artisan would have discovered the optimum amount of the propylene glycol suitable for midazolam by routine experimentations. The skilled artisan would have had a reasonable expectation of successfully producing a stable propylene glycol based nasal composition in admixture with polyethylene glycol because Mukae teaches that the latter is suitable thickener for enhancing the retentivity of a medicine on the nasal mucosae.

Claim 29 is rejected under 35 U.S.C. 103(a) as being unpatentable over Schweizer, Hjortkjaer and Haslwanter over claim 11, 13, 15, 18, 28 as above, and further in view of Knoester et al. (Br. J. Clin. Pharmacol. 53, 501-507).

The combined references fail to teach a midazolam intranasal composition comprising no less than 25 mg/ml of midazolam or its salts.

Knoester teaches administering intranasal preparation comprising 5mg/mL in a mixture of water and propylene glycol. See p. 502, Methods. The reference teaches that the dose of intranasal midazolam for treating seizure activity is based on body weight, and increasing the concentration of midazolam reduces the total volume of fluid to be delivered, thereby maintaining the bioavailability and efficacy of the drug. See p. 502, first column, first 2 paragraphs.

It would have been obvious to one of ordinary skill in the art to modify the teachings of the combined references by increasing the concentration of midazolam or its salts as motivated by Knoester, because the latter teaches that increasing the midazolam

concentration to meet the required dose is more effective than increasing the amount of the fluid.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 11-15, 18, and 27 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3, 6, 8-11, 19, 21, 23, 24, and 27 of US 6610271 in view of Schweizer (US 5,166,202).

The '271 patent claims a sedative-anxiolytic nasal composition comprising lorazepam; 15-25 % by volume of polyethylene glycol and 75-85 % by volume of propylene glycol; and a sweetener. See '271, claims 1, 3, 6, 8, 10, and 11. PEG 400 is used in the examples that are defined in the specification. See instant claim 27.

While the patent claims a nasal formulation for lorazepam and a method of treating anxiety-related disorders by using the composition, the patent does not teach midazolam.

Schweizer, as discussed above, teaches a method of treating panic disorder, panic attacks and the prevention of panic attacks to reduce anxiety by nasally administering midazolam and its pharmaceutically acceptable salts. See instant claim 3. The reference teaches administering 1-4 drops of an aqueous solution of midazolam, which is equivalent to 0.05-0.2 ml of the active ingredient. See col. 4, lines 41 – 53; instant claims 4 and 7. The reference teaches a nasal suspension in col. 3, lines 63-66, meeting instant claim 7. Inducing general anesthesia by administering midazolam with other anesthetic agent is also taught. See col. 3, lines 8 – 10; instant claims 8 and 15. The reference teaches that a relatively low dosage of midazolam is required for the treatment, and that the drug is well tolerated and easily administered. See col. 5, line 46 – col. 7, line 24.

It would have been obvious to one of ordinary skill in the art at the time of the present invention to modify the '271 invention by substituting lorazepam with midazolam because 1) both are art-recognized equivalents since they are well known anxiolytic drugs which are intranasally administered; and 2) Schweizer teaches that midazolam nasal spray is effective even in low dosage, well tolerated and easily administered. The skilled artisan would have had a reasonable expectation of successfully producing a similar nasal composition for reducing anxiety. It is also viewed that the obvious variation of the prior arts, which would comprise midazolam in a nasal carrier

comprising polyethylene glycol and propylene glycol as required by the present invention, would naturally have the metabolism rate as defined in the present claims 16-19.

Claims 16, 17, 20, and 28 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3, 6, 8-11, 19, 21, 23, 24, and 27 of '271 and Schweizer as applied to claims 11-15, 18, and 27 as above, and further in view of Fisgin.

The '271 patent and Schweizer does not teach the time required for midazolam to take effects.

Fisgin discloses a method of rapidly treating acute seizures of children in 5 minutes by nasally administering midazolam (5 mg/mL). See abstract.

It would have been obvious to a skilled artisan to formulate and administer the midazolam nasal spray of the combined references as motivated by Fisgin because the latter teaches the time required for midazolam that is nasally administered to take effects. The skilled artisan would have had a reasonable expectation of successfully determining the dosage of midazolam and the time required to treat acute by nasally administering midazolam.

Claim 29 is rejected under 35 U.S.C. 103(a) as being unpatentable over claims 1, 3, 6, 8-11, 19, 21, 23, 24, and 27 of '271 and Schweizer as applied to claims 11-15, 18, and 27 as above, and further in view of Knoester et al. (Br. J. Clin. Pharmacol. 53, 501-507).

The combined references fail to teach a midazolam intranasal composition comprising no less than 25 mg/ml of midazolam or its salts.

Knoester is discussed above.

It would have been obvious to one of ordinary skill in the art to modify the teachings of the combined references by increasing the concentration of midazolam or its salts as motivated by Knoester, because the latter teaches that increasing the midazolam concentration to meet the required dose is more effective than increasing the amount of the fluid.

Claims 11-15, 18, and 27 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-24 of U.S. Pat. Application No. 11/376979 in view of Schweizer (US 5,166,202).

The '979 application claims a sedative-anxiolytic nasal composition comprising lorazepam; 15-25 % by volume of polyethylene glycol 400 and 75-85 % by volume of propylene glycol.

The copending application does not claim a midazolam nasal composition.

Schweizer is discussed above.

It would have been obvious to one of ordinary skill in the art at the time of the present invention to modify the '979 invention by substituting lorazepam with midazolam because 1) both are art-recognized equivalents since they are well known anxiolytic drugs which are intranasally administered; and 2) Schweizer teaches that midazolam

nasal spray is effective even in low dosage, well tolerated and easily administered. The skilled artisan would have had a reasonable expectation of successfully producing a similar nasal composition for reducing anxiety. It is also viewed that the obvious variation of the prior arts, which would comprise midazolam in a nasal carrier comprising polyethylene glycol and propylene glycol as required by the present invention, would naturally have the metabolism rate as defined in the present claims 16-19.

Claims 16, 17, 20, and 28 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-24 of '979 application and Schweizer as applied to claims 11-15, 18, and 27 as above, and further in view of Fisgin.

The copending application and Schweizer do not teach the time required for midazolam to take effects.

Fisgin discloses a method of rapidly treating acute seizures of children in 5 minutes by nasally administering midazolam (5 mg/mL). See abstract.

It would have been obvious to a skilled artisan to formulate and administer the midazolam nasal spray of the combined references as motivated by Fisgin because the latter teaches the time required for midazolam that is nasally administered to take effects. The skilled artisan would have had a reasonable expectation of successfully determining the dosage of midazolam and the time required to treat acute by nasally administering midazolam.

Claim 29 is rejected under 35 U.S.C. 103(a) as being unpatentable over claims 1-24 of '979 application and Schweizer as applied to claims 11-15, 18, and 27 as above, and further in view of Knoester et al. (Br. J. Clin. Pharmacol. 53, 501-507).

The combined references fail to teach a midazolam intranasal composition comprising no less than 25 mg/ml of midazolam or its salts.

Knoester is discussed above.

It would have been obvious to one of ordinary skill in the art to modify the teachings of the combined references by increasing the concentration of midazolam or its salts as motivated by Knoester, because the latter teaches that increasing the midazolam concentration to meet the required dose is more effective than increasing the amount of the fluid.

Response to Arguments

Applicant's arguments filed on January 31, 2008 have been fully considered but they are not persuasive in part and moot in view of new grounds of rejection in part.

Applicant argues that each of the references fails to disclose using about 15-25 % by volume of polyethylene glycol. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant argues that '832 teaches away from using about 15 -25 % by volume of polyethylene glycol. The argument is unpersuasive because it is viewed that there is no significant or nonobvious difference between up to about 10 % and the lower limitation of the claimed range, about 15 %.

Applicant argues that '375 patent and Fisgin fail to disclose midazolam and a formulation containing 15-25 % by volume of polyethylene glycol. The argument is unpersuasive because these limitations have been addressed by the primary reference and the '832 patent.

Applicant also argues that one of ordinary skill in the art would not have added midazolam to the carrier of the '832, '375, and '639 patents because these teach using ingredients other than midazolam. The argument is unpersuasive because the issue is whether adding the presently claimed glycol solvent and carrier to the invention of Schweizer, the primary reference, would have been obvious. The contents of the formulations of the secondary references need not be incorporated into the midazolam nasal spray of Schweizer. Furthermore, applicant's claims do not exclude the presence of ingredients other than midazolam.

Applicant's argument regarding claim 29 is moot in view of the new rejections made above.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gina C. Yu whose telephone number is 571-272-8605.

The examiner can normally be reached on Monday through Friday, from 8:00AM until 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Gina C. Yu/
Patent Examiner